

REMARKS

Applicants have amended the claims, and added claims, as discussed more fully below in response to the outstanding Office Action. None of the claims amendments or additions constitutes new matter.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 16-17, 20, 23-24, 26-37 and 40-48 stand rejected under 35 U.S.C. § 112, first paragraph, on the asserted basis that "the specification, while being enabling for DNA sequences of defined sequence composition, does not reasonable provide enablement for sequences defined solely by the property of hybridization, as coding for unspecified portions of proteins, degenerate sequences, or sequences defined as complementary where no specificity of hybridization is defined." More particularly, the Examiner contends that "the specification does not teach or provide guidance to allow one to determine the composition of diverse sequences which hybridize under high criteria, code for undefined portions of polypeptides and does not teach how one might use fragments of undefined length of such sequences or which comprise degenerate sequences to those sequences." According to the Examiner, "[I]n failing to provide such guidance it would require a trial and error process for one of ordinary skill in the art to determine sequences which have the stated utility disclosed in the specification -- to serve as hybridization probes useful for

HLA-typing or as sources of recombinant proteins which are antigenic. Applicants request that the Examiner withdraw this rejection, in view of the claim amendments and reasons outlined below.

In further discussing the § 112, first paragraph rejection (see page 10 of the Office Action), the Examiner states that "[t]he main issues of concern ... in the rejection made are that the methods recited never clearly recite the selectivity or specificity of hybridization." Pursuant to the Examiner's suggestion and reference to acceptable claim language in claim 31, applicants have amended the claims to further define the hybridizing DNA sequences useful according to this invention as those which "specifically hybridize" to the particular DNA sequences enumerated therein.

The Examiner also contends that, with respect to the claims directed to fragments, "there is no recitation of either a minimum size fragment or the functional properties of the fragment; the claims encompass a large genus of fragments which are not useful as well as those which might be" (pages 10-11 of the Office Action). Based on this contention, the Examiner states that this aspect of the rejection may be overcome by reciting with more particularity the nature of the fragments.

By virtue of the amendments discussed above, the claims which refer to DNA sequences encoding portions of the polypeptides encoded by the DNA sequences enumerated therein

further define the DNA sequences those which specifically hybridize to the enumerated DNA sequences. See, for example, subpart (d) of claim 23 and 24. With respect to claims 23 and 24 and their dependent claims, those DNA sequences are also defined as encoding a portion comprising a region of mismatch between any two of the enumerated DNA sequences. With respect to claim 31 and its dependent claims, those DNA sequences are also defined as those which specifically hybridize to an HLA-DR- β -chain locus. With respect to claims 32 and 33 and their dependent claims, those DNA sequences are also defined as those which specifically hybridize to an HLA Class II β -chain locus. The nature of the claimed portions is recited with particularity. Claims 34-37 further define the DNA sequences of subpart (d) of claims 23-24. Accordingly, the fragments recited in claims 34-37 are characterized by the features of the DNA sequences of subpart (d) of claims 23-24, i.e., they encode a portion comprising a region of mismatch between any two of the DNA sequences enumerated in claims 23-24 and they specifically hybridize to the enumerated DNA sequences.

With applicants' disclosure in hand, and in view of knowledge in the art as of the effective filing date of this application, one of skill in the art could readily prepare DNA sequences, other than those of specifically "defined sequence composition", useful for HLA-DR and HLA typing processes and kits. As of applicants' filing date,

one of skill in the art would appreciate that, in any specific DNA typing kit or typing process, the useful DNA sequences are those that selectively hybridize to the DNA sequence of interest. It would also be routine for one of skill in the art to determine the length of a DNA sequence that will specifically hybridize to a particular DNA sequence in the human genome. Thus, once provided with a particular DNA sequence, such as those of "defined sequence composition" recited in the claims, one of skill in the art would readily be able to prepare other DNA sequences or fragments of those DNA sequences that would specifically hybridize to DNA of interest.

As part of their disclosure, applicants determined and compared the nucleotide sequence of DNA sequences DR- β -A and DR- β -B (the sequences of which are disclosed in Figures 5A-5D, 7 and 7A) and identified nucleotide sequence differences that, upon expression, code for regions of amino acid mismatch between the polypeptides encoded by those sequences. See, e.g., specification, page 32, lines 1-8 and Figure 9. Specifically, these regions are defined by amino acids 8-15, 26-32 or 72-78, or amino acids 39-45.

Applicants further identified the first three regions as polymorphic regions among different HLA-DR- β -chain genes. The fourth region was identified as a conserved region. Once applicants identified such regions, they also made possible portions of the DNA sequences encoding such regions which are capable of specifically hybridizing to said

regions, as well as DNA sequences which are complementary or degenerate thereto.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 23-24 and 31 stand rejected under 35 U.S.C. § 112, second paragraph, on the basis that certain phrases render the claims "vague and indefinite." Applicants have obviated the objection to each phrase by amendment.

The Examiner contends that in step (c) of the claim 23, "it is not clear what the recitation of 'high criterium' means." Applicants have amended claim 23, as well as other claims reciting the objected-to phrase, to replace it with the phrase "specifically hybridizing."

The Examiner contends that claims 23 and 31 are "indefinite in the recitation of 'DNA sequences which, as a result of the genetic code, are degenerate to' as it is not clear 'what degenerate to means.'" Applicants have amended the claims to replace the objected-to phrase with the phrase "DNA sequences which differ from the foregoing sequences in codon sequence due to the degeneracy of the genetic code", as suggested by the Examiner.

Claims 16, 41-42 and 44 stand rejected under 35 U.S.C. § 112, second paragraph, "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps." The Examiner contends that the omitted steps are a step which completes the preamble of the claim,

i.e., a comparing step by which the results of the hybridization are actually used to determine an HLA-type."

Applicants have obviated this rejection by amending HLA-DR typing process claims 16, 41, 42 and 44 relate to incorporate the further step of comparing any detected hybridization to hybridization between DNA of known HLA-DR type and said DNA sequences (former claims 43, 45 and 48).

Applicants have added claims 49-50, which recite processes for detecting HLA DR- β -chain DNA in a DNA sample, comprising the steps of hybridizing the sample DNA to a DNA sequence according to any one of claims 23-24 and 34-39 or claims 31-33 and detecting hybridization between said DNA and said DNA sequence. Such processes are described in the specification at page 29, line 9 to page 32, line 30.

The added claims focus on the heart of one facet of applicants' invention -- discovery of the utility of the recited DNA sequences to determine HLA-DR specificity of a given sample at the DNA level, using hybridization techniques.

The Double Patenting Rejection

Claims 16, 17, 20 and 22-47 stand rejected under the doctrine of obviousness-type double patenting as being "unpatentable over" claims 1-22 of United States patent 5,169,941. Applicants stand ready to file a Terminal

Disclaimer in this application, if appropriate, upon the Examiner's indication of allowable subject matter.

Applicants acknowledge, with appreciation, the Examiner's withdrawal of the previous rejection of claims 23-24, 26 and 31-38 under 35 U.S.C. § 101, in view of the amendments thereto, to recite "isolated" DNA sequences.

Supplemental Information Disclosure Statement

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), applicants make of record the following document, a copy of which is submitted herewith:*

United States Patent

5,503,976 (Mach et al.) issued April 2, 1996

Applicants respectfully request that the above-cited document be (1) fully considered by the Examiner during the course of the examination of this application and (2) printed on any patent issuing from this application.

Applicant also requests that a copy of the enclosed Form PTO-1449, duly initialed by the Examiner, be forwarded to the undersigned with the next official communication.

This Statement is being submitted in conjunction with applicants' Request Under 37 C.F.R. § 1.129(a) to Withdraw Finality of the outstanding Office Action and its accompanying fee. Accordingly, applicants do not believe

* For the Examiner's convenience, applicants have enclosed a completed Form PTO-1449, listing this document.

that a separate fee under 37 C.F.R. 1.17(p) is required, as the Statement is not being submitted pursuant to 37 C.F.R. § 1.97(c). Nevertheless, in the Transmittal Letter accompanying this Statement, applicants have authorized the Commissioner to charge any fee required by 37 C.F.R. § 1.17 to Deposit Account No. 06-1075.

Applicants' representatives believe that a telephonic interview may facilitate allowance of this application and intend to contact the Examiner shortly to arrange for such an interview.

Applicants request that the Examiner consider the foregoing amendments and remarks and pass this application to issue.

Respectfully submitted,

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